Object, Space, and Object-Space Representations in the Primate Hippocampus

Edmund T. Rolls, Jianzhong Xiang, and Leonardo Franco
Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

Rolls, Edmund T., Jianzhong Xiang, and Leonardo Franco. Object, space, and object-space representations in the primate hippocampus. *J Neurophysiol* 94: 833–844, 2005. First published March 23, 2005; doi:10.1152/jn.01063.2004. A fundamental question about the function of the primate including human hippocampus is whether object as well as allocentric spatial information is represented. Recordings were made from single hippocampal formation neurons while macaques performed an object-place memory task that required the monkeys to learn associations between objects and where they were shown in a room. Some neurons (10%) responded differently to different objects independently of location; other neurons (13%) responded to the spatial view independently of which object was present at the location; and some neurons (12%) responded to a combination of a particular object and the place where it was shown in the room. These results show that there are separate as well as combined representations of objects and their locations in space in the primate hippocampus. This is a property required in an episodic memory system, for which associations between objects and the places where they are seen are prototypical. The results thus provide an important advance by showing that a requirement for a human episodic memory system, separate and combined neuronal representations of objects and where they are seen "out there" in the environment, is present in the primate hippocampus.

INTRODUCTION

Event or episodic memory (Tulving 1972) refers to the memory of particular events or episodes. A prototypical episodic memory might include a particular combination of information about the objects or faces present and where they were. Medial temporal lobe damage in humans, frequently including the hippocampus, can severely impair episodic memory (Corkin et al. 1997; Scoville and Milner 1957; Squire and Knowlton 2000), and object-place memory in monkeys provides a model of this in that episodic memories prototypically include associations between spatial or contextual and object information (Gaffan 1994).

An issue fundamental for understanding the functions of the hippocampus and medial temporal lobe structures in event or episodic memory is whether they have the required spatial and object or face representations and whether they combine this information in such a way that unique combinations of an object and the place where it was shown are provided. For these questions to be answered, neuronal recording is necessary, because this is the only direct way to show whether there are separate representations of objects, locations " out there" in space (termed "places" in this paper), and particular combinations of objects and their places. The rat hippocampus contains place cells, which respond to the place where the rat is located (McNaughton et al. 1983; O'Keefe and Speakman 1987).

However, place cells are not useful for the primate (including human) episodic memory task of remembering where out there in the environment a particular object or place was seen, because they respond to where the animal is located. The discovery of single neurons in the primate (macaque) hippocampus that respond to the position in space out there currently being viewed (Robertson et al. 1998; Rolls 1999; Rolls et al. 1997a, 1998) was therefore important, because these neurons provide a representation that is ideal for association with an object to form an object-place episodic memory. Spatial view cells represent allocentric information in that they respond to the spatial view provided that the monkey looks at the location in space, and independently of the monkey's location in the room, or whether the spatial view is to the monkey's left or right (Georges-Francois et al. 1999).

Although an appropriate spatial representation is present in the primate hippocampus and parahippocampal gyrus for object-place memory, and there is much spatial information represented in the primate hippocampus (Ono et al. 1993; Rolls 1999), there is little evidence on whether objects are also represented by neurons in the primate hippocampus, and no evidence on whether single hippocampal neurons respond to particular combinations of object and spatial view (or "place out there") information. It is crucial to know whether such neurons are present in the primate hippocampus, for the simplest implementation of an episodic memory involves associating together by synaptic modification separate representations of objects and places to form neurons that respond to combinations of objects and places (Marr 1971; Rolls 1989, 1996; Rolls and Treves 1998; Rolls et al. 2002). Previous research has not answered these questions, as summarized in DISCUSSION.

METHODS

In this study, we addressed the fundamental questions raised in the Introduction by recording from single hippocampal and perirhinal cortex neurons while monkeys performed an object-"place out there" memory task. In the task, shown in Fig. 1*D*, the monkey saw two monitors at different locations ("out there") in the room with the head held to point in a fixed direction providing the view indicated. If a square was shown on the left monitor, the monkey could lick to obtain fruit juice reward. If the square was shown on the right monitor, the monkey had to avoid licking, otherwise a taste of aversive saline was obtained. If a triangle was shown on the right monitor, the monkey could lick to obtain fruit juice reward. If the triangle was shown on the left monitor, the monkey had to avoid licking; otherwise a taste of aversive saline was obtained. The task thus required the monkey to

---

Address for reprint requests and other correspondence: E. T. Rolls, Dept. of Experimental Psychology, Univ. of Oxford, Oxford OX1 3UD, UK (E-mail: Edmund.Rolls@psy.ox.ac.uk).

Object-related activity

(Neuron = BP045c4a)

A Neuronal responses

B Object-related firing

C Eye position

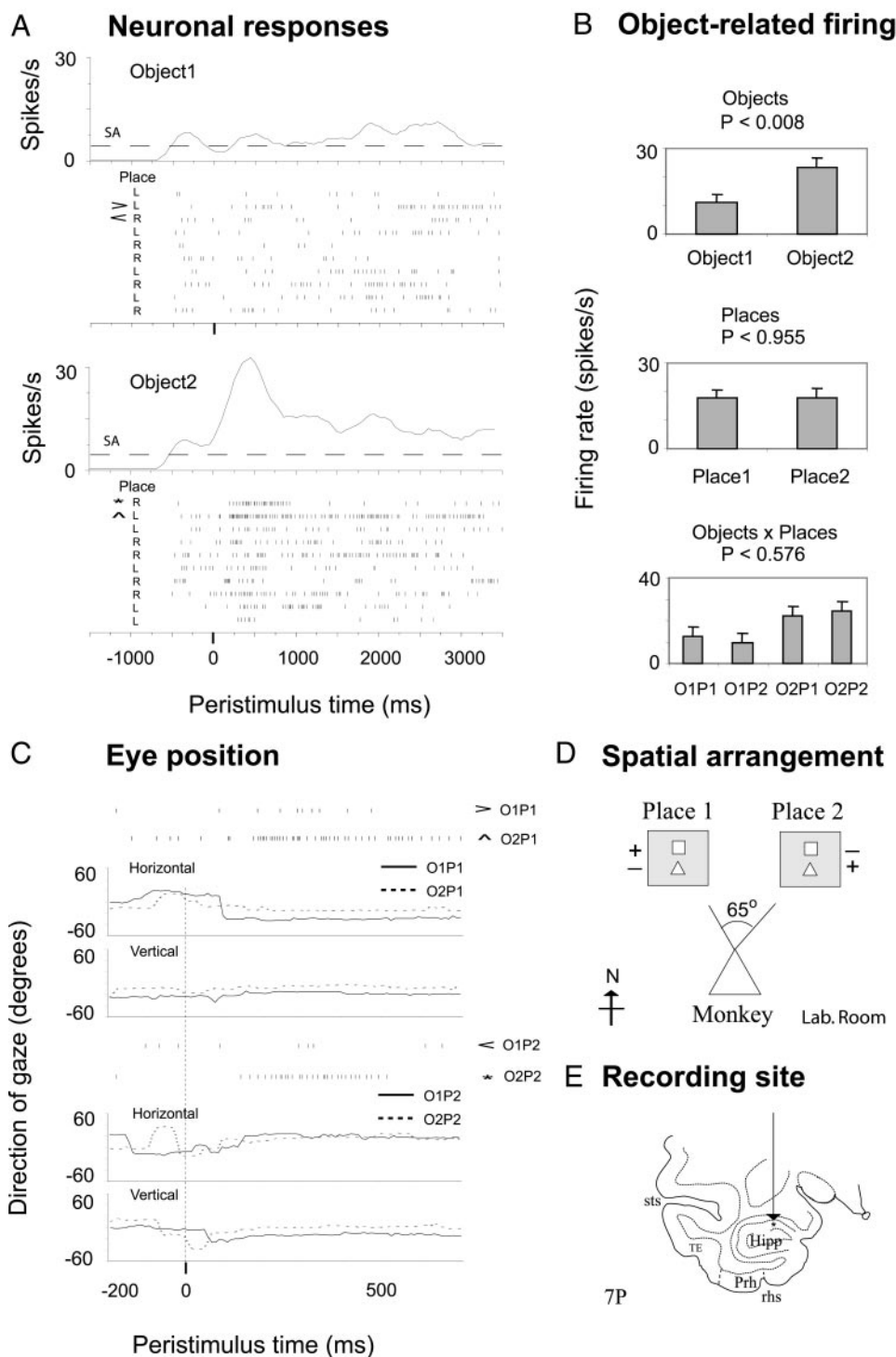## D Spatial arrangement

E Recording site

FIG. 1. Neuron with object-related firing. *A*: peristimulus time histograms and rastergrams showing response of neuron BP045c4a to objects 1 and 2. Each rastergram shows firing on a single trial. Rastergrams start 500 ms before onset of the visual stimuli at *time 0*, and peristimulus time histogram was smoothed with a Gaussian filter with a SD of 150 ms. L, object was shown on the left, place 1; R, object was shown on the right, place 2; SA, spontaneous activity. *B*: firing rate response of the neuron on different trials sorted according to object that was shown on the trial, place where the object was shown, and combination of which object was shown with the place where it was shown. In the object × position bar histograms, O1P1 = object 1 in place 1, etc. The mean responses ± SE are shown. *C*: trials to show eye positions on 4 different trials. The 4 trials correspond to trials indicated with the corresponding symbol in *A*. *D*: schematic diagram showing spatial arrangement used in the Go-NoGo object-place combination task in this experiment. +, a Go (lick) response to that object-place combination will be rewarded; −, it will be punished. Only 1 object was shown on the screen at a time. The room was approximately 4 × 4 m, and the distance of the monkey from monitors was typically 1.5–2 m in the different experiments. Triangle-labeled monkey shows position of the monkey, and angle shows approximate angle subtended by video display monitors. *E*: recording site of neuron in CA1. Hipp, hippocampus; Prh, perirhinal cortex; rhs, rhinal sulcus; sts, superior temporal sulcus; TE, inferior temporal visual cortex; 7P, 7 mm posterior to the sphenoid reference.

learn about object-place combinations. Neither the left or the right nor the triangle or the square were differentially associated with reward or punishment. The task enabled us to determine whether there were hippocampal and related neurons just to the place out there (the left vs. the right position in the room); just to object (the triangle vs. the square); or to unique combinations of these (e.g., the triangle only

when it was shown on the left, which is the type of information needed to solve the object-place memory task). New images replacing the triangle and square were introduced frequently (often daily) to ensure that new object-place associations were being learned regularly and were thus likely to require and engage medial temporal lobe structures.

Object-place memory task

The task is shown in Fig. 1D. On each trial, an image of an object was shown on one of the two video monitors, which could be moved to different places in the room. This enabled one of the monitors to be placed in the spatial view field of the neuron being recorded, and the other to be placed outside the spatial view field. Examples of the arrangements used to facilitate this are shown in Figs. 1D–3D, and this is made explicit in Fig. 5. The monkey was thus every day moved to different locations in the room, encouraging the use of allocentric (room-based) spatial coordinates by the monkey, and enabling allocentric spatial encoding by the neurons to be distinguished from egocentric as described previously (Feigenbaum and Rolls 1991; Georges-Francois et al. 1999). The equiluminant images were for initial testing on a day a triangle and square, as shown in Fig. 1, but were changed on a daily basis to different images of real objects, so that new combinations of objects and places had to be learned by the monkey, and the task could not be performed on a purely habit or conditional (object + place)-to-response basis (see Rolls and Treves 1998). This was also ensured by placing the monitors and the monkey in different places in the room several times each day. The digitized images of real objects had a resolution of 256×256 and 256 grayscale levels. Of the neurons with differential responses described here, typically no more than three neurons were recorded on the same day. If object 1 was shown in place 1, the monkey could lick a tube placed in front of its mouth to obtain fruit juice reward. If object 1 was shown in place 2, the monkey was required not to lick the tube; otherwise, a drop of mildly aversive saline was obtained. If object 2 was shown in place 2, the monkey could lick a tube placed in front of its mouth to obtain fruit juice reward. If object 2 was shown in place 1, the monkey was required not to lick the tube; otherwise, a drop of mildly aversive saline was obtained. The monkey thus had to learn that a combination of a particular object in one place in the room was associated with reward and of the same object in a different place was associated with saline. The task could thus be described as a Go/NoGo object-and-place-combination task. Each object and each place were equally associated with reward, so that object-reward or place-reward associations could not be used to solve the task. The computer permuted in random sequences the equiprobable object that was chosen for any given trial, and the equiprobable place that was chosen for the trial. The black and white images of objects were 10×8 cm, and, given the distances of the monitors, which were typically 1–4 m from the monkey, typically subtended ~ 5.7–$1.4°$ at the retina.

The timing of the task was as follows. After an intertrial interval of 2 s, one of the monitors was indicated as being active by placing a gray scale 0.5 (127/255) background on it. At this time, the monkey typically saccaded to look at that monitor, as shown by the scleral search coil eye position recordings. Within 1 s, a 0.5-s, 500-Hz trial warning cue sounded. At the end of this period, at *time 0*, an object was shown on the selected monitor for 1.5 s, and the monkey could lick to obtain fruit juice if the reward-associated object-place combination applied. Because multiple licks could be made for fruit juice during the period in which the visual stimulus was on, the monkey was already fixating the monitor before the object was shown, because this enabled more licks for fruit juice to be made on the trial. Fixation of the monitor and processing of the visual stimuli were confirmed by the performance of the monkeys, which was typically 90% correct during the recordings in the object-place memory task. The intertrial interval started after the image was turned off.

Recordings

Single neurons were recorded with epoxylite insulated tungsten microelectrodes (FHC, Bowdinham, MA) with impedances of 1–5 MOhm and giving a high signal to noise ratio of $\geq 3:1$ with well-isolated neurons from two rhesus macaques (4–7 kg) with methods that have been described previously (Rolls et al. 1989) and the references cited above. All procedures, including preparative and subsequent ones, were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and were licensed under the UK Animals (Scientific Procedures) Act 1986. Every time that the cell fired, that time was recorded with an accuracy of 1 ms. Discovery spike acquisition software (Datawave, Boulder, CO) was used during the recordings, and its spike cluster cutting software was used off-line to ensure that the spikes of well-isolated neurons were analyzed.

Procedures

The single neuron microelectrode was lowered until just above the hippocampus, and each neuron encountered was monitored to test whether it had the large amplitude, well-isolated action potential with a low spontaneous firing rate (Rolls et al. 1998), and peak firing rate of typically 10 but ≤ 20 spikes/s, which is typical of hippocampal spatial view cells and is thought to be produced by hippocampal pyramidal cells (Georges-Francois et al. 1999; Robertson et al. 1998; Rolls et al. 1997b, 1998). Tests were performed for any spatial view sensitivity of the cell, by the experimenter moving to different locations in the room and showing the monkey food so that the monkey looked to that location in the room. If spatial view sensitivity was found (as described and analyzed in the papers just cited and revealed by the neuron firing when the monkey looked at some locations in the room and not others), one of the monitors was placed in a part of the spatial view field where there was a high response (mean rate = 13.8 spikes/s for hippocampal neurons with place-related firing) relative to their spontaneous firing rate (mean rate = 8.2 spikes/s), and the other monitor was placed in a part of the spatial view field where there was a relatively low response (mean rate = 8.6 spikes/s, close to the spontaneous rate). If no spatial view field was found by the preliminary testing, the monitors were placed at arbitrary positions in the room. (Even if a neuron did not have a spatial view field, it was nevertheless possible that the neuron might respond to a combination of an object and a spatial view.) The object-place task was run for typically 80 trials, providing 20 trials for every object-place combination. After recording in the hippocampus, recording typically continued until the microelectrode reached the base of the brain, so that neuronal activity in the perirhinal cortex and related areas such as TF could also be measured and analyzed during the same task.

Statistics

The neuronal activity for each cell was analyzed for a 1-s period starting 100 ms after the visual stimulus was turned on, because the monkey was processing the visual stimulus and making the decision about whether to respond in this period. A two-factor ANOVA was performed to determine whether the cell had significantly different firing rates when the trials were sorted according to each of the hypotheses, where one factor was object and the second factor was place. The hypotheses were that the cell had different firing rates for each object (independently of place); for each place (independently of object); or between the different combinations of object and place, as reflected in a significant interaction term in the two-factor ANOVA. The results of this two-way ANOVA were used to classify the cells into those responding differently to different objects, those responding differently to different places, and those responding to combinations of object and place. As a follow-up test, to assess which firing rate values were different from the others, a one-way ANOVA was performed for the different object-place combinations, and this was followed by two-tailed LSD posthoc tests as implemented in SPSS and corrected for multiple comparisons. Fisher exact probability tests as described in the Results were performed to check that the number of significant neuronal responses found could not have arisen by chance.

Recording sites

X-radiography was used to determine the position of the micro-electrode after each recording track relative to permanent reference electrodes and to the anterior sphenoidal process, a bony landmark whose position is relatively invariant with respect to deep brain structures. Microlesions (60–100 μA, 100 s) made through the tip of the recording electrode during the final tracks were used to mark the location of typical neurons. These microlesions together with the associated X-radiographs allowed the position of all cells to be reconstructed in the 50-μm brain sections with the methods described in Feigenbaum and Rolls (1991). As described previously, the spatial view cells typically had low spontaneous firing rates, low peak firing rates, and large amplitude broad spikes (Rolls et al. 1997b). Other cells had faster spontaneous and peak firing rates (often in the range of 20–60 spikes/s) and small amplitude short spikes. Taking into account findings in the rat, e.g., Fox and Ranck (1989), it is likely that the large slow spiking cells are pyramidal cells and the fast firing small amplitude cells are interneurons. All the hippocampal neurons described here had the large amplitude relatively low firing rate type of activity, and were recorded in regions in which there are pyramidal cells. They are sometimes referred to for brevity as pyramidal cells in this paper, but the criteria for inclusion in this category are those just given.

RESULTS

It was possible to complete the data collection required for detailed analyses described below for 453 visually responsive neurons in the hippocampus and posterior part of the perirhinal cortex and adjoining TF cortex in two rhesus macaques (267 neurons in BL and 186 in BP). First, we describe the types of neuronal response found in the task, and then we summarize the findings for the population of neurons analyzed.

Neurons responding differently to different objects

Figure 1 shows the experiments performed on one neuron (BP045c4a) with object-related activity. The spatial arrangement of the testing is shown in Fig. 1D. Figure 1B shows the firing rate of the neuron when sorted according to object (independently of place, *top*), place (independently of object, *middle*), and into object × place (*bottom*). Significant differences of firing rate were found only when the data were sorted according to object. (The P values for each test are shown above each analysis. The test for significant object × place effects is a significant interaction term in the 2-way ANOVA for object × place.) These data were obtained from all trials in which object 1 or object 2 were shown independently of place. None of these cells classified as showing object-related firing had significantly different firing rates when all the trials were sorted according to the place in the room where the objects

were shown, or a significant interaction term when sorted to provide the mean response for each object when shown in each place (object × place). To provide further evidence on the nature of the neuronal responses to the objects, rastergrams and peristimulus time histograms of the neuronal responses of the neurons to the two objects are shown in Fig. 1A. The neuron has a clear visual stimulus evoked response to object 2 with a latency of ∼180 ms. For some of the trials in Fig. 1A, object 2 was in the left place in the room (L), and on other trials in the right place in the room (R). To provide further evidence on the nature of the neuronal responses, eye position recordings are shown in Fig. 1C. Four trials are shown, and correspond to four of the trials in Fig. 1A as shown by the symbols (>, <, etc). The eye position plots show that when the object was being shown on the left monitor at P1, the monkey looked at P1, and that when the objects were shown on the right monitor at P2, the monkey looked at P2. The continuation of the firing after stimulus offset shown on some trials in Fig. 1A occurred when the monkey continued to look at the spatial view field after the visual stimulus on the monitor was turned off. This was common for spatial view neurons. Figure 1C shows that the neuron responds to the object being shown, independently of the position of the object in the room (i.e., the neuron responds to O2P1 and O2P2, but not to O1P1 or O1P2).

It is shown in Table 1 that 10.4% (47/453) of neurons in the hippocampus and posterior perirhinal/adjoining TF cortex responded differentially to the two objects. All these neurons had statistically significant differences between objects at $P < 0.05$ (with 28/47 significant at $P < 0.01$, and 9/47 at $P < 0.001$). Of these 47 neurons, 9 neurons also had significant object × place effects. We checked that the significant results for object 1 versus object 2 obtained for these neurons were not due to chance by calculating a Fisher exact probability of obtaining the number of significant results across the ANOVAs performed on the whole population of 453 neurons. This check showed that, across the 453 neurons, the z value was 6.60 associated with the hypothesis that this number of results with the significance level of each test that was obtained in the ANOVA would have been obtained by chance, and thus the hypothesis that the results were due to chance statistical fluctuations can be rejected with $P < 10^{-9}$. The mean firing rate (±SE) of the population of these neurons to the more effective object was 15.0 ± 1.3 (median 14.7) spikes/s, and to the less effective object was 8.5 ± 0.9 (median 8.3) spikes/s. Neurons with responses that differed to the two objects but not to place were found in both the hippocampus (CA3 and CA1), and in the posterior perirhinal/TF cortex, as shown in Table 1, and the proportions in each region were not significantly different (as

TABLE 1. *Numbers of neurons of each type among the 453 cells analyzed in the hippocampus and posterior part of the perirhinal cortex/anterior parahippocampal gyrus area TF*

	Total	Differential		Object		Place		Object × Place	
Regions	n	n	Percent	n	Percent	n	Percent	n	Percent
Hippocampus	306	100	32.7	32	10.5	38	12.4	30	9.8
Posterior perirhinal cortex/TF	147	59	40.1	15	10.2	21	14.3	23	15.6
Total	453	159	35.1	47	10.4	59	13.0	53	11.7

Percentages shown for each neuron type are expressed relative to the total number of 453 neurons analyzed. The object, place, and object × place categories are not mutually exclusive, as described in the text.

shown by a χ^2 test on the data shown in Table 1). The objects were often different in different experiments, but if the same object was used in different experiments, the different neurons had no tendency to respond to the same object.

Neurons responding differently to different places in the room

Figure 2 shows analyses of the responses of a neuron that responded differently to different places in the room independently of object. The conventions are similar to those in Fig. 1. Figure 2B shows that the neurons had different firing rates for the different places that were independent of which object that was shown at the place. The testing arrangement is shown in Fig. 2D. Figure 2C confirms that when the monkey was looking at place 2 the neuron fired, and moreover fired independently of which object was shown at that place. Figure 2, A and C, shows that the neuron responded with a latency of ~120 ms after the monkey looked to place 2 but not when he looked to place 1. (In both cases, there was an object being shown on the screen, and in a sense was part of the view being seen, but the neuron did not fire differently depending on which object was present on the screen, as shown in Fig. 2B.) The different neurons responded to different places in the room, and this is why the testing arrangement was adjusted, as shown by difference between Figs. 1D and 2D. The number of hippocampal neurons with higher firing to the contralateral compared with the ipsilateral place was 18, and vice versa was 22. The number of posterior perirhinal cortex neurons with higher firing contralaterally was 9, and ipsilaterally was 12. There was no significant difference between these proportions responding contralaterally versus ipsilaterally, as shown by χ^2 tests. None of the neurons classified in this way had significant differences when the trials were sorted according to object, or to object × place, and this is shown in Fig. 2B for one of the neurons.

Table 1 shows that 13.0% (59/453) of neurons in the hippocampus and posterior perirhinal/TF cortex responded differentially to the two places (at $P < 0.05$, with 32/59 significant at $P < 0.01$, and 11/59 at $P < 0.001$). Of these 59 neurons, 6 neurons also had significant object × place effects. A Fisher exact probability test enabled rejection of the hypothesis that the significant results across the 453 neurons for viewing place 1 versus place 2 were due to chance and obtained a z value of 7.53 ($P < 10^{-9}$). The mean firing rate of the population of these neurons to the more effective place was 14.8 ± 1.1 (median, 16.1) spikes/s, and to the less effective place was 9.4 ± 0.8 (median 9.7) spikes/s. Neurons with responses that differed to the two places viewed but not to object were found in both the hippocampus (CA3 and CA1), and in the posterior perirhinal cortex, as shown in Table 1, and the proportions in each region were not significantly different (as shown by a χ^2 test on the data).

Neurons responding to combinations of the object and its place in the room

Figure 3 shows the activity of one neuron that responded to a particular combination of an object and a place in the room. Figure 3B shows the activity of the neuron with the trials sorted according to object, place, and object × place. The neuron

responded primarily to object 1 when it was in place 1 (O1P1), and the object × place interaction was significant as shown. Figure 3, A and B, documents this further, with the same conventions as in Fig. 1. The neuron responded with a latency of ~150 ms whenever object 1 was presented in place 1, but had no significant evoked activity to the other combinations of object and place. (The apparent ramp up of activity before *time 0* in Fig. 3A was due to the temporal smoothing and the fact that data collection started 500 ms before the visual stimuli were shown. The neuron shown in Fig. 3 did not respond to object-reward associations, in that O1P1 and O2P2 were both associated with reward, yet the neuron responded only to the O1P1 combination. Furthermore, no neurons in this study had activity that occurred differently based only on rewarded vs. nonrewarded trials.)

For inclusion in this group, the neurons had a statistically significant interaction in a two-way ANOVA with object and place as factors and no significant difference between objects or between places. Table 1 shows that 11.7% (53/453) of neurons in the hippocampus and posterior perirhinal cortex responded differentially to different object × place combinations (at $P < 0.05$, with 25/53 significant at $P < 0.01$, and 12/53 at $P < 0.001$). Of these 53 neurons, 9 neurons also had significant object effects, and 6 neurons had significant place effects. A Fisher exact probability test enabled rejection of the hypothesis that the significant results across the 453 neurons for object × place interaction effects were due to chance and obtained a z value of 2.639 ($P < 0.01$). The mean firing rate of the population of these neurons to the most effective object-place combination was 15.9 ± 1.1 (median, 16.3) spikes/s, and to the least effective object-place combination was 8.1 ± 0.8 (median, 8.9) spikes/s. Neurons with significant object × place interaction effects were found in both the hippocampus (CA3 and CA1), and in the posterior perirhinal/TF cortex, as shown in Table 1, and the proportions in each region were not significantly different (as shown by χ^2 test = 2.08, df = 1, $P > 0.1$).

Summary of population of neurons recorded and the recording sites

The numbers of neurons with each type of effect are shown in Table 1. Neurons that responded differentially to object, to the place being viewed, and to object × place were found in both the hippocampus and the posterior perirhinal/TF cortex. No difference in the proportion of each type of neuron in these two brain regions was found (as shown by $\chi^2 = 1.5$, df = 2, $P > 0.3$). Because, as noted above, 15 neurons had significant effects of more than one type (9 object × place and object, 6 object × place and place), the total number of neurons in the sample of 453 that had one or more significant effects was 144, or 31.8% of the sample of neurons.

No neurons were found that responded only on reward or only on nonreward trials. Thus none of these neurons encoded reward. (Such a neuron might in this study have responded for example to object 1 on the left and object 2 on the right, which were both rewarded, and not to object 2 on the left and object 1 on the right, which were both associated with punishment.) This is also a useful statistical check on the data and provides evidence that the neuronal responses found were not due to chance statistical occurrences during the 80 trials.

Place-related activity

(Neuron = BP054c1a)

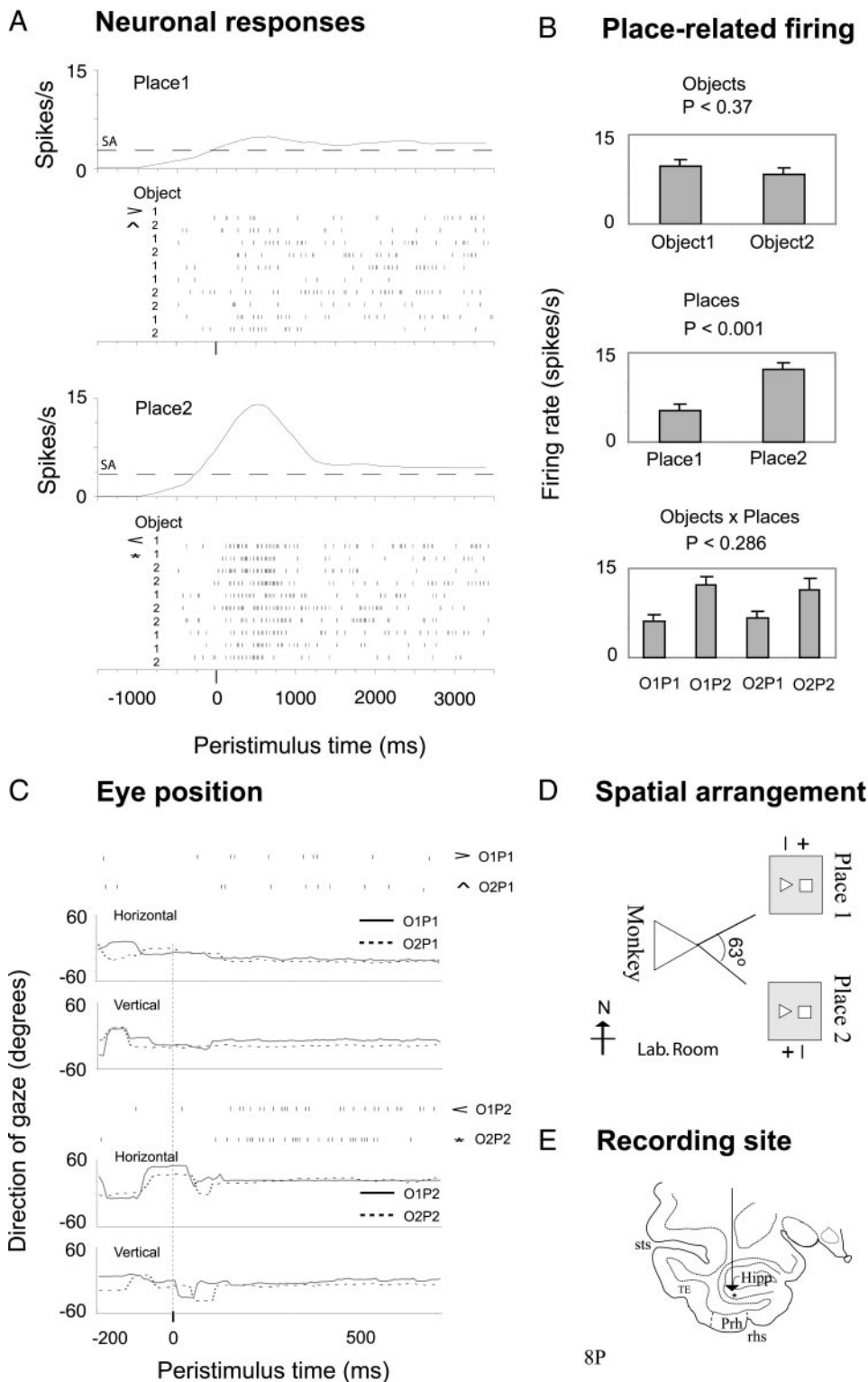## A Neuronal responses

B Place-related firing

FIG. 2.   A neuron (BP054c1a) with place-related firing. Conventions as in Fig. 1, except that in *A*, the 2 peristimulus time histograms are for different places. *E*: recording site of the neuron in CA3.

C Eye position

D Spatial arrangement

E Recording site

The sites at which the different types of neuron were recorded are shown in Fig. 4. The transition between perirhinal cortex and the parahippocampal gyrus was as defined by Suzuki and Amaral (2003). This places the boundary between the perirhinal cortex and the parahippocampal gyrus areas TF and TH at ~9 mm posterior to sphenoid in the coordinate

Object AND Place-related activity

(Neuron = BL003c8a)

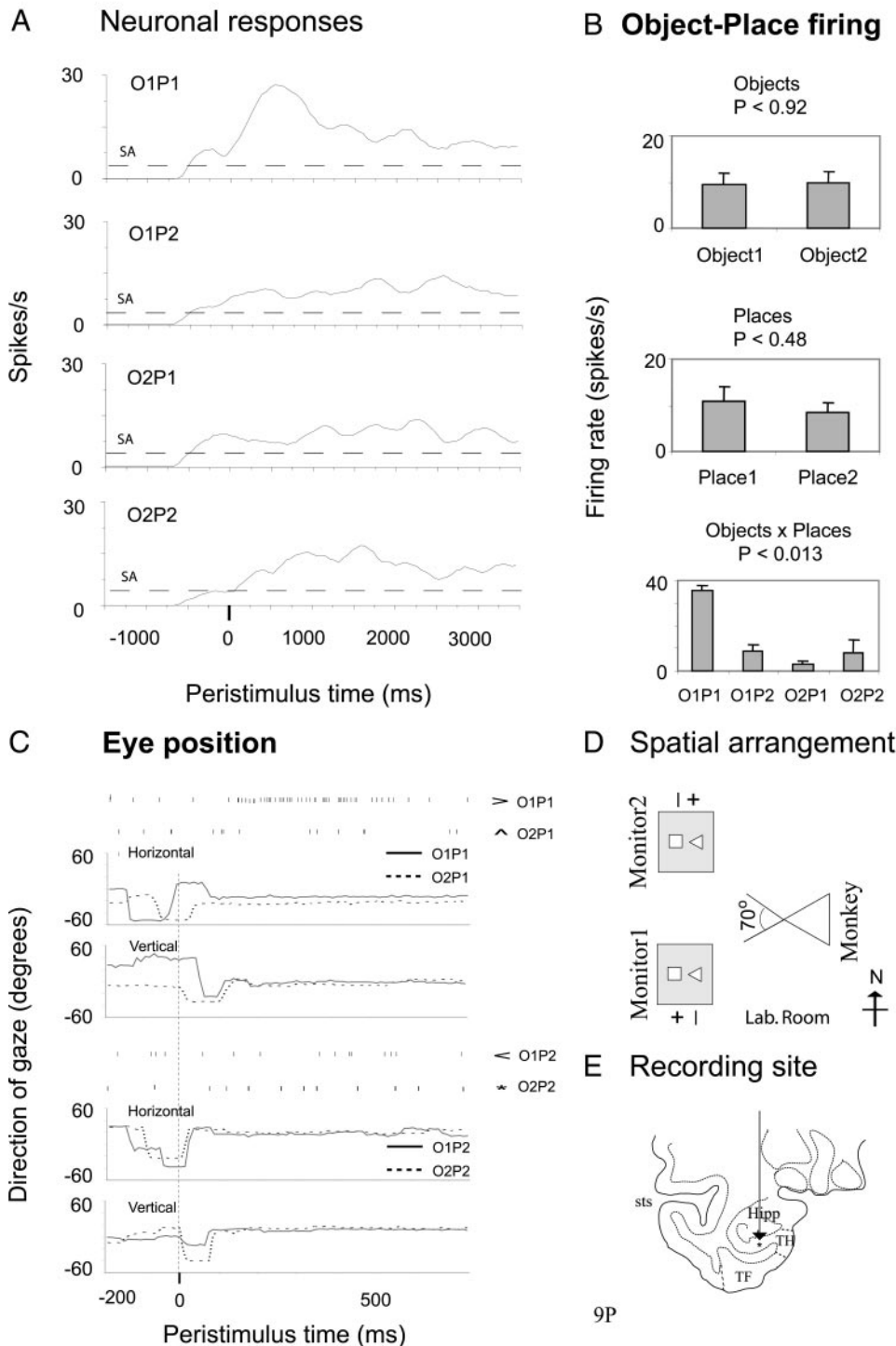## A Neuronal responses

B Object-Place firing

FIG. 3. A neuron (BL003c8a) with firing occurring to a particular combination of an object and place (O1P1). Conventions as in Fig. 1, except that in *A,* the 4 peristimulus time histograms are for each object-place combination. *E*: recording site of the neuron in hippocampus.

C Eye position

D Spatial arrangement

E Recording site

system shown in Fig. 4, developed by Rolls and colleagues (Aggleton and Passingham 1981). All the neurons in the perirhinal cortex recorded in this study were at the posterior end of the perirhinal cortex, which is within 3 mm of its posterior border. We note that in our monkey brains, the anterior border of the perirhinal cortex is at ~6 mm anterior to sphenoid. The perirhinal recordings in this study were thus in the posterior 20–25% of the perirhinal cortex, and the recordings in TF were in its most anterior one mm (see Fig. 4). Given that these neurons were in a 4-mm region at the posterior end

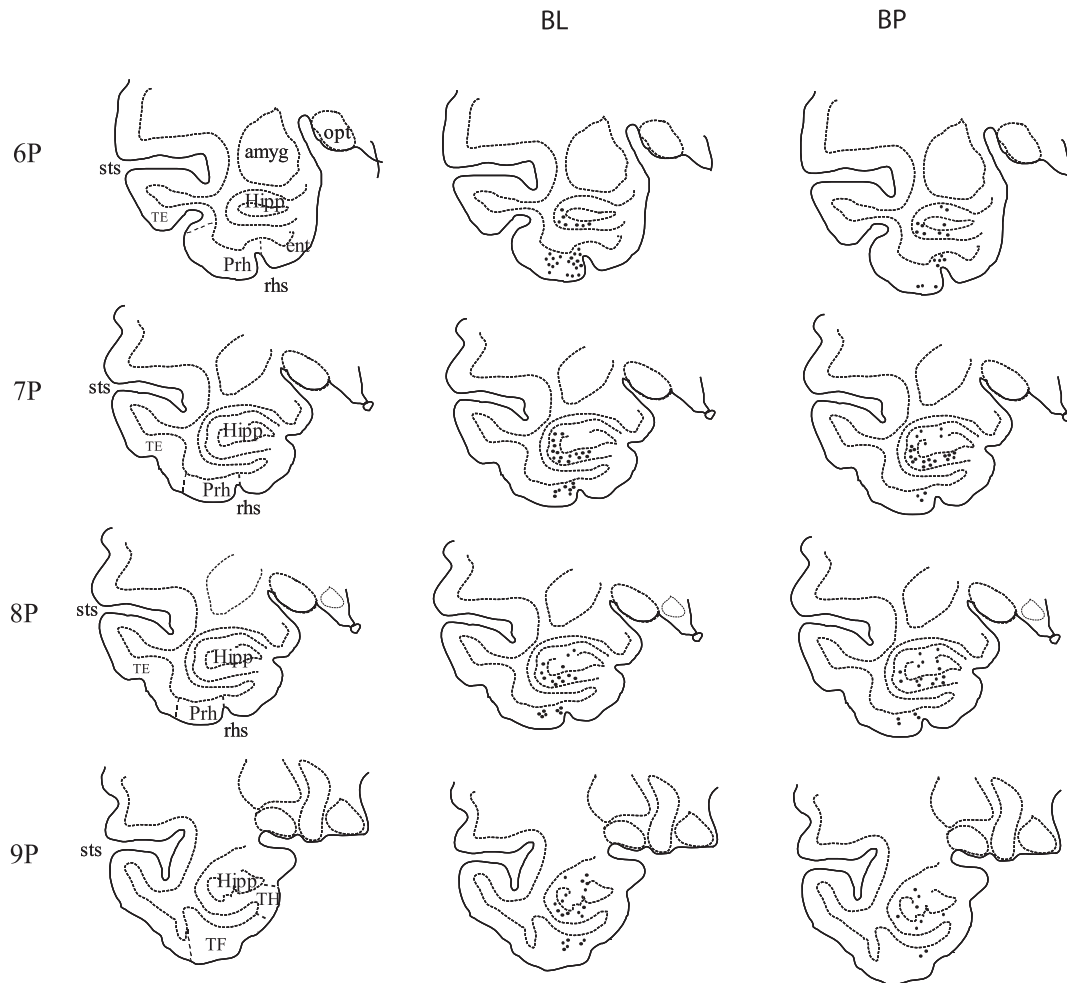## Location of differential neurones

FIG. 4. Recording sites. Hippocampal and parahippocampal sites at which different spatial view cells were recorded. Coronal sections at different distances in mm posterior (P) to the sphenoid reference are shown. Amyg, amygdala; his, hippocampal sulcus; Hipp, hippocampal pyramidal cell field CA3/CA1 and dentate gyrus; opt, optic tract; Prh, perirhinal cortex; rhs, rhinal sulcus; sts, superior temporal sulcus; TE, inferior temporal visual cortex; TF/TH, areas of the parahippocampal gyrus; BL, recordings from macaque BL; BP, recordings from macaque BP.

of the perirhinal cortex and the anterior part of area TF, we have described these neurons as being in the posterior perirhinal/TF cortex, as shown in Table 1.

The mean spontaneous firing rate of the differential neurons recorded in the hippocampus was 8.1 ± 12 (SD) spikes/s, and the mean peak evoked response was 19.6 ± 18 spikes/s. The mean spontaneous firing rate of the differential neurons recorded in the posterior part of the perirhinal cortex was 10.9 ± 20 spikes/s, and the mean peak evoked response was 27.1 ± 26 spikes/s. The mean spontaneous firing rate of the differential neurons recorded in area TF was 9.6 ± 6 spikes/s, and the mean evoked response was 16.4 ± 10 spikes/s.

Although previous studies have shown that spatial view cells of the type analyzed here have allocentric spatial representations (Robertson et al. 1998; Rolls 1999; Rolls et al. 1997a, 1998), and the aim of this study was primarily to investigate neuronal activity in an object-place memory task rather than to

analyze the spatial representations in the primate hippocampus because this was done in the previous studies, we did perform checks on a number of the new neurons included in this study that the representation was in allocentric coordinates when it was about place. We did this by the type of experiment shown in Fig. 5. When the monkey and video display units were in the room locations shown in Fig. 5A (top), the neuron responded with a higher firing rate when any object was shown in place 1 than in place 2 in the room. In Fig. 5A, place 1 happened to be on the monkey's left. When the monkey and video display units were in the room locations shown in Fig. 5B (top), the neuron responded with a higher firing rate when any object was shown in place 1 than in place 3 in the room. In Fig. 5B, place 1 happened to be on the monkey's right. Thus the neuron was not firing in egocentric coordinates, but instead in allocentric (i.e., world or room-based) coordinates. That is, the neuron responded whenever the monkey looked at place 1 in the room,

Neuronal responses
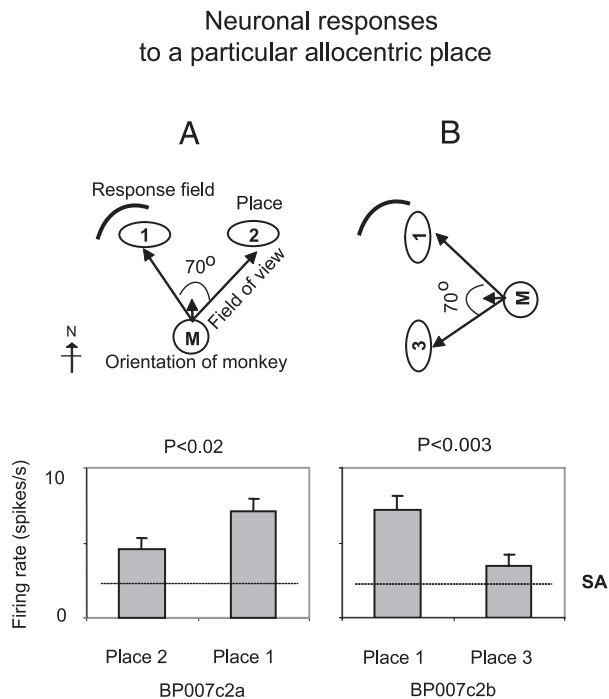## to a particular allocentric place

FIG. 5. Effect of altering arrangement of the monkey and video display units in the room. Allocentric places of display units in the room are labeled 1, 2, and 3. Neuron responded whenever a stimulus was shown at place 1, independently of whether the monitor was on the monkey's (egocentric) right or left. The mean responses ± SE are shown. SA, spontaneous firing rate.

independently of whether that was on the monkey's left or right.

It was possible to complete this further extensive testing to analyze the coordinate system being used in 38 neurons with place-related firing. Of these, 25 (66%) were shown to have allocentric encoding of the type shown in Fig. 5. This represents a very considerable increase in the sample of neurons proven to have this type of room-based allocentric encoding in the hippocampal formation (Georges-Francois et al. 1999). For eight of the place neurons (21%) studied here, the encoding was in egocentric coordinates, with the neuron responding more for example whenever the stimulus was shown on the monkey's left than on the monkey's right, independently of the place in the room of the stimuli or the head direction of the monkey neurons. Egocentric spatial representations have been described previously in the macaque hippocampus (Feigenbaum and Rolls 1991). For the remaining five neurons, one change of the testing arrangement was insufficient to provide an unambiguous assessment of the coordinate system being used. Of the 38 neurons with place-related firing on which these studies of the coordinate systems being used were performed, 24 were in the hippocampus, 13 were in the perirhinal cortex, and 1 was in TF. The proportions of the neurons with different types of encoding were not significantly different in these regions.

Although it was not an important part of the study described here, we note that the relation between the preliminary testing for spatial view fields by moving the monkey to look at different places in the room and the types of responsiveness found in the object-place memory task were as follows. Of the 59 neurons in Table 1 with place-related activity in the object-place memory task, 43 (73%) had evidence of spatial view field

sensitivity in the preliminary testing. Of the 53 neurons with object $\times$ place-related activity in the task, 42 (79%) had evidence of spatial view field sensitivity in the preliminary testing. These proportions were not different ($\chi^2 = 0.3$, df = 1, not significant). Of the 47 neurons with object-related activity in the task, 15 (32%) had evidence of spatial view field sensitivity in the preliminary testing. This proportion was significantly lower than that for neurons with place-related activity ($\chi^2 = 16.1$, df = 1, $P < 0.001$), and for neurons with object $\times$ place-related activity ($\chi^2 = 20.9$, df = 1, $P < 0.001$). Thus if a neuron had evidence in the preliminary testing of spatial view sensitivity, it was more likely in the object-place task to have place or object $\times$ place than object-related activity. It is noted that there is not expected to be a 1:1 relation between the preliminary testing (in which spatial view fields might be on the walls of the room) and the object-place testing, where the monitors are necessarily within the room.

DISCUSSION

The results show that, in the primate hippocampus, there are neurons that respond to objects, to places being viewed, and to combinations of objects and the places being viewed in an object-place memory task. The task is prototypical of human event memory in that where an object is in space "out there" is what is being remembered. The results provide the first evidence that there are not only spatial view cells, which are ideal for providing an allocentric representation of space "out there" (Georges-Francois et al. 1999), but also object cells, and neurons that respond to combinations of objects and their position out there. The results thus provide important new evidence relevant to theories of hippocampal function that include an autoassociation network (Rolls 1989, 1996; Rolls and Treves 1998; Treves and Rolls 1994), for these predict separate object, place, and object-place combination neurons in the same network. The results also provide much new evidence for many hippocampal and related neurons that the encoding is allocentric room-based, as shown by the type of experiment shown in Fig. 5 and described in the last two paragraphs of RESULTS.

The design of the experiment enabled it to show that some neurons respond to particular combinations of objects and their position " out there." By using in any one recording session from a neuron just two objects and two spatial locations, it was possible to show that different neurons responded to all possible combinations of these, that is, to object 1-in-place 1, object 1-in-place 2, object 2-in-place 1, and object 2-in-place 2. This is exactly what is required of a memory system that can use Hebbian associativity to form arbitrary associations between objects and places, based on their co-occurrence. By regularly changing the objects and places (with new images of objects being introduced sometimes every day during the course of the experiments), we ensured that new learning was required and that fixed overlearned habits could not be used to perform the object-place memory task. The design of the task also ensured that the task could not be solved by object-reward or place-reward association learning, because each object and place were equally associated with reward. It was each of the four object-place associations that were unique.

Previous research has not answered these questions about whether objects, places "out there," and object-place combina-

tions are represented by primate hippocampal neuronal activity in an association learning task in which associations between particular objects and particular locations in space "out there" must be learned. It has been shown that in a task in which the monkey must perform novelty-familiarity discriminations for whether an object has been seen before in a quadrant of a screen, some hippocampal neurons responded differently on the novel/familiar trials, but neurons were not described that responded only to particular objects in particular quadrants of the screen (Rolls et al. 1989). In the entorhinal cortex (the hippocampus was not studied), Suzuki and Amaral (2003) showed that some neurons respond to objects in a delayed match to object task, and other neurons respond to places on a screen in a delayed match to place task, but did not study whether object-place "out there" neurons were found in an object-place memory task. Some rat hippocampal neurons respond to odors (Wood et al. 1999), but spatial locations "out there" are not apparently represented in the rat hippocampus, so this does not address how humans could remember which object they have seen in which spatial location, a characteristic of human episodic memory. In humans, some hippocampal formation neurons respond to objects (Fried et al. 1997; Kreiman et al. 2000), but the humans were not performing associative memory between objects and their allocentric position in space, nor was the location being viewed measured with eye position recordings.

In the autoassociation network of the type postulated to be present in the CA3 region of the hippocampus (Rolls 1989, 1996; Rolls and Treves 1998; Treves and Rolls 1994), the discrete representation that is typical of objects must be associated with the continuous representation that is typical of spatial representations, and Rolls et al. (2002) have shown that this model does operate without difficulty using associative learning between the object and spatial representations. It is interesting that not all the neurons become object-place neurons because of this associativity, but some remain as object neurons, and others as spatial view neurons, probably due to the statistical properties of the connections onto each neuron, whereby some neurons are probabilistically more likely to be strongly influenced by object inputs, others by spatial inputs, and others by both (Treves and Rolls 1992, 1994). This factor operates in a scenario where the sparseness of the representation in the hippocampus is kept relatively low, both to keep the storage capacity high, and to make sure that not all hippocampal neurons become activated by just a few objects, spatial views, or particular combinations of them (Rolls 1996; Rolls and Treves 1998; Treves and Rolls 1991, 1992, 1994). We believe that the object-place combination neurons described here provide the useful and necessary input to regions outside the hippocampus, which are able to form associations of any particular combination with either reward or punishment.

The hippocampal neurons with object, place, and object-place combination tuning may be important in the object-place memory task, with the CA3 neurons providing a single network where the associatively modifiable recurrent collateral synaptic connections between the neurons could enable arbitrary object-place associations to be formed (Debanne et al. 1998; Rolls 1989, 1996; Rolls and Treves 1998; Treves and Rolls 1992). Consistent with this, neurotoxic lesions that selectively damage the primate hippocampus impair spatial scene memory (Murray et al. 1998). Although one-trial memory for

object-place associations was severely impaired by aspiration of the hippocampus (Parkinson et al. 1988), the same task was not impaired by neurotoxic lesions of the hippocampus, although impairments were produced by posterior parahippocampal lesions (Malkova and Mishkin 2003). First, we note that a factor here is that the one-trial task used by Malkova and Mishkin is relatively easy (in that each object is shown on just one trial, and the "spatial scene" is very simple), and hippocampal damage is more likely to impair tasks if more than one item must be remembered (Angeli et al. 1993), consistent with the hypothesized role of the hippocampus when many items must be remembered (Rolls and Treves 1998; Treves and Rolls 1994). Hippocampal damage may also tend to produce larger impairments with complex spatial scenes. Second, we note that in this study, many parahippocampal gyrus neurons did have activity specifically related to the object-place association memory task, as shown in Table 1. The pathways for visual inputs about objects to reach the hippocampus are probably via the inferior temporal visual cortex, perirhinal cortex, and entorhinal cortex, and the parahippocampal gyrus (areas TF and TH) may be important for the spatial as well as object information. The hippocampal neurons described here were found mainly in the anterior half of the hippocampus as shown in Fig. 4, and this was where we searched, for it is possible that the perirhinal cortex projects via entorhinal cortex more strongly to anterior parts of the hippocampus. The hippocampal neurons were mainly in CA3 and CA1.

The perirhinal cortex itself is implicated in object recognition memory, tested in for example delayed match to sample memory tasks which may require a memory for many seconds and a number of intervening stimuli (Buckley and Gaffan 2000; Murray and Bussey 1999). It has previously been well established that the perirhinal cortex, which has strong inputs from the inferior temporal cortical areas in which neurons respond to objects (Rolls 2000b; Rolls and Deco 2002), also has neurons that respond differentially to objects, and that are involved in short term memory tasks (Hölscher and Rolls 2002; Richmond and Optican 1987). In addition to its functions in object recognition memory, and in some perceptual functions (Buckley et al. 2001), it has now been found that the perirhinal cortex contains neurons that reflect the long-term familiarity of visual stimuli, with neuronal responses to objects that gradually increase over the course of several hundred 1-s presentations (Hölscher et al. 2003). We have thus proposed that part of the medial temporal lobe syndrome in which patients report that stimuli no longer seem familiar to them arises because of damage to the perirhinal cortex long-term familiarity system for objects. This is a distinct function from episodic memory, which requires unique and arbitrary associations between for example objects, faces, and places.

The issue then arises about why some perirhinal cortex neurons in this study contained not only object, but also place and object and place combination, neurons. The answer may lie in the fact that the neurons in this study in the cortex below the hippocampus were in a 4-mm region at the posterior end of the perirhinal cortex, and the anterior part of area TF (which is part of the parahippocampal cortex), which may be a transitional region. (We have for this reason described them as being the posterior perirhinal/TF cortex, as shown in Table 1.) Anatomical evidence indicates that the perirhinal cortex has its main visual afferent connections from visual areas such as TE

(inferior temporal cortex) (Lavenex and Amaral 2000; Suzuki and Amaral 1994a,b) and is therefore conceived as being mainly object-related and involved in object working memory, perceptual functions, and long-term familiarity memory (Buckley and Gaffan 2000; Buckley et al. 2001; Hölscher and Rolls 2002; Hölscher et al. 2003; Murray and Bussey 1999), whereas the parahippocampal cortex area TF has its main visual afferent connections from the posterior parietal cortex (Lavenex and Amaral 2000; Suzuki and Amaral 1994a,b) and is therefore conceived as being spatial and being involved in event memory of which space is a typical component (Buckley and Gaffan 2000; Rolls 1999). The findings described here indicate that the cortical region at the boundary of the perirhinal and parahippocampal cortex is functionally transitional, with both visual object, visual place, and object-place cells. Furthermore, the responses of the posterior perirhinal cortex neurons could reflect information backprojected from the hippocampus where the object-place combination neurons may be formed, particularly when the associations must be large in number, and between arbitrary objects and places (Rolls 2000a). In any case, an important point established in this paper is that in the hippocampus itself, which may be important for episodic memory, neurons do respond in an object-place memory task to objects, to places out there, or to combinations of objects and places.

In relation to previous findings, we believe that this is the first study to investigate primate hippocampal neuronal activity in an object-place memory task, where the space represented was that relevant to much human event and episodic memory, that is, allocentric space out there. The findings provide strong evidence that representations of objects, as well as of allocentric locations of space "out there" by spatial view cells, are present in the primate hippocampus. The findings also show that neurons are present in the primate hippocampus that respond to unique combinations of objects and places out there, as would be expected and required in an associative memory system that forms unique associations between objects and places. The findings thus provide an important part of the evidence on what is represented in the primate hippocampus, and are important in understanding how episodic memories may be formed in humans.

GRANTS

REFERENCES

Aggleton JP and Passingham RE. Stereotaxic surgery under X-ray guidance in the rhesus monkey, with special reference to the amygdala. *Exp Brain Res* 44: 271–276, 1981.

Angeli SJ, Murray EA, and Mishkin M. Hippocampectomized monkeys can remember one place but not two. *Neuropsychologia* 31: 1021–1030, 1993.

Buckley MJ, Booth MC, Rolls ET, and Gaffan D. Selective perceptual impairments after perirhinal cortex ablation. *J Neurosci* 21: 9824–9836, 2001.

Buckley MJ and Gaffan D. The hippocampus, perirhinal cortex, and memory in the monkey. In: *Brain, Perception, and Memory: Advances in Cognitive Neuroscience*, edited by Bolhuis JJ. Oxford: Oxford, 2000, p. 279–298.

Corkin S, Amaral DG, Gonzalez RG, Johnson KA, and Hyman BT. HM's medial temporal lobe lesion: findings from magnetic resonance imaging. *J Neurosci* 17: 3964–3979, 1997.

Debanne D, Gähwiler BH, and Thompson SM. Long-term synaptic plasticity between pairs of individual CA3 pyramidal cells in rat hippocampal slice cultures. *J Physiol* 507: 237–247, 1998.

Feigenbaum JD and Rolls ET. Allocentric and egocentric spatial information processing in the hippocampal formation of the behaving primate. *Psychobiology* 19: 21–40, 1991.

Fox SE and Ranck JBJ. Electrophysiological characteristics of hippocampal complex-spike cells and theta cell. *Exp Brain Res* 41: 399–410, 1989.

Fried I, MacDonald KA, and Wilson CL. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 18: 753–765, 1997.

Gaffan D. Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. *J Cogn Neurosci* 6: 305–320, 1994.

Georges-Francois P, Rolls ET, and Robertson RG. Spatial view cells in the primate hippocampus: allocentric view not head direction or eye position or place. *Cereb Cortex* 9: 197–212, 1999.

Hölscher C and Rolls ET. Perirhinal cortex neuronal activity is actively related to working memory in the macaque. *Neural Plasticity* 9: 41–51, 2002.

Hölscher C, Rolls ET, and Xiang J-Z. Perirhinal cortex neuronal activity related to long-term familiarity memory in the macaque. *Eur J Neurosci* 18: 2037–2046, 2003.

Kreiman G, Koch C, and Fried I. Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat Neurosci* 3: 946–953, 2000.

Lavenex P and Amaral DG. Hippocampal-neocortical interaction: a hierarchy of associativity. *Hippocampus* 10: 420–430, 2000.

Malkova L and Mishkin M. One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. *J Neurosci* 23: 1956–1965, 2003.

Marr D. Simple memory: a theory for archiocortex. *Phil Trans Roy Soc Lond B* 262: 23–81, 1971.

McNaughton BL, Barnes CA, and O'Keefe J. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52: 41–49, 1983.

Murray EA, Baxter MG, and Gaffan D. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. *Behav Neurosci* 112: 1291–1303, 1998.

Murray EA and Bussey TJ. Perceptual-mnemonic function of the perirhinal cortex. *Trends Cogn Sci* 3: 142–151, 1999.

O' Keefe J and Speakman A. Single unit activity in the rat hippocampus during a spatial memory task. *Exp Brain Res* 68: 1–27, 1987.

Ono T, Tamura R, Nishijo H, and Nakamura K. Neural mechanisms of recognition and memory in the limbic system. In: *Brain Mechanisms of Perception and Memory: From Neuron to Behavior*, edited by Ono T, Squire LR, Raichle ME, Perrett DI, and Fukuda M. New York: Oxford, 1993, p. 330–355.

Parkinson JK, Murray EA, and Mishkin M. A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. *J Neurosci* 8: 4059–4167, 1988.

Richmond BJ and Optican LM. Temporal encoding of two-dimensional patterns by single units in primate inferior temporal cortex. II. Quantification of response waveform. *J Neurophysiol* 57: 147–161, 1987.

Robertson RG, Rolls ET, and Georges-François P. Spatial view cells in the primate hippocampus: effects of removal of view details. *J Neurophysiol* 79: 1145–1156, 1998.

Rolls ET. Functions of neuronal networks in the hippocampus and neocortex in memory. In: *Neural Models of Plasticity: Experimental and Theoretical Approaches*, edited by Byrne JH and Berry WO. San Diego, CA: Academic Press, 1989, p. 240–265.

Rolls ET. A theory of hippocampal function in memory. *Hippocampus* 6: 601–620, 1996.

Rolls ET. Spatial view cells and the representation of place in the primate hippocampus. *Hippocampus* 9: 467–480, 1999.

Rolls ET. Hippocampo-cortical and cortico-cortical backprojections. *Hippocampus* 10: 380–388, 2000a.

Rolls ET. Memory systems in the brain. *Annu Rev Psychol* 51: 599–630, 2000b.

Rolls ET and Deco G. *Computational Neuroscience of Vision*. Oxford: Oxford, 2002.

Rolls ET, Miyashita Y, Cahusac PMB, Kesner RP, Niki H, Feigenbaum J, and Bach L. Hippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. *J Neurosci* 9: 1835–1845, 1989.

Rolls ET, Robertson RG, and Georges-François P. Spatial view cells in the primate hippocampus. *Eur J Neurosci* 9: 1789–1794, 1997a.

Rolls ET, Stringer SM, and Trappenberg TP. A unified model of spatial and episodic memory. *Proc R Soc Lond B* 269: 1087–1093, 2002.

Rolls ET and Treves A. *Neural Networks and Brain Function.* Oxford: Oxford, 1998.

Rolls ET, Treves A, Robertson RG, Georges-François P, and Panzeri S. Information about spatial view in an ensemble of primate hippocampal cells. *J Neurophysiol* 79: 1797–1813, 1998.

Rolls ET, Treves A, Tovee MJ, and Panzeri S. Information in the neuronal representation of individual stimuli in the primate temporal visual cortex. *J Comput Neurosci* 4: 309–333, 1997b.

Scoville WB and Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20: 11–21, 1957.

Squire LR and Knowlton BJ. The medial temporal lobe, the hippocampus, and the memory systems of the brain. In: *The New Cognitive Neurosciences*, edited by Gazzaniga MS. Cambridge, MA: MIT Press, 2000, p. 765–779.

Suzuki WA and Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey—cortical afferents. *J Comp Neurol* 350: 497–533, 1994a.

Suzuki WA and Amaral DG. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J Neurosci* 14: 1856–1877, 1994b.

Suzuki WA and Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cytoarchitectonic and chemoarchitectonic organisation. *J Comp Neurol* 463: 67–91, 2003.

Treves A and Rolls ET. What determines the capacity of autoassociative memories in the brain? *Network* 2: 371–397, 1991.

Treves A and Rolls ET. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus* 2: 189–199, 1992.

Treves A and Rolls ET. A computational analysis of the role of the hippocampus in memory. *Hippocampus* 4: 374–391, 1994.

Tulving E. Episodic and semantic memory. In: *Organisation of Memory*, edited by Tulving E and Donaldson W. New York: Academic Press, 1972 p. 381–403.

Wood ER, Dudchenko PA, and Eichenbaum H. The global record of memory in hippocampal neuronal activity. *Nature* 397: 613–616, 1999.